CDMRP

Department of Defense

Breast Cancer Research Semipostal Program





U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

History of the CDMRP

In 1992, the Office of the Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Created within the U.S. Army Medical Research and Materiel Command to manage these critical funds, the CDMRP has grown to encompass multiple targeted programs and has received more than $6 billion in appropriations from its inception in fiscal year 1993 (FY93) through FY10. Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs such as the Breast Cancer Research Program (BCRP) is allocated via specific guidance from Congress.

Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation, with both tiers involving a dynamic interaction among scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of proposals measured against established criteria determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel, which compares proposals to each other and makes funding recommendations based on scientific merit, portfolio composition, and relevance to program goals.

Partnerships

Partnerships between consumers and scientists are an integral component of several CDMRP processes. Consumers and scientists are partners that participate on:

- Peer review panels to provide expert advice on the scientific merit and potential impact of proposals
- The Integration Panel to make programmatic recommendations for the program's vision, investment strategies, and funding selections to reflect the needs of both the consumer and research communities.

Breast Cancer Research Semipostal Program

Breast Cancer Research Semipostal Program

Due to the efforts of breast cancer advocates, the Stamp Out Breast Cancer Act (Public Law 105-41 [H.R. 1585]) led to the U.S. Postal Service's issuance of a new first-class stamp, the Breast Cancer Research Semipostal (BCRS). The stamp, which costs 55¢, can be purchased on a voluntary basis by the public. Net revenues from sales of the BCRS are provided to two designated funding agencies, the DOD BCRP and the National Institutes of Health, to support breast cancer research.

Research and Management Cost Allocations

Since the BCRS was issued in 1998, the monies received by the DOD BCRP through FY10 have been used to fully or partially fund 43 Idea Awards and 3 Synergistic Idea Awards **(Figure 1)**. Both award mechanisms support highly innovative, high-risk, high-reward research that could lead to critical discoveries in breast cancer. As with all BCRP awards, proposals funded through the BCRS Program are reviewed according to the two-tiered review system.

Total Proceeds from BCRS	$20,931,948.89
Research	$19,018,757.11
Management Costs	$908,358.67

Figure 1A. BCRS Research and Management Cost Allocation for FY99–FY09

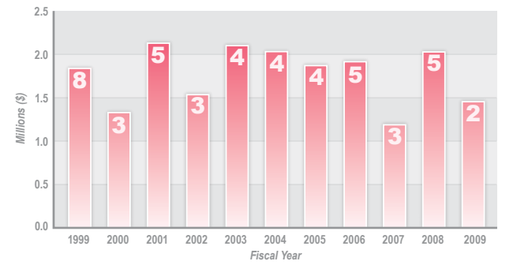


Figure 1B. BCRS Installments and Number of Awards Funded by Fiscal Year

Portfolio Composition

The BCRS Program supports research from diverse disciplines. An evaluation of the awards funded through the BCRS shows that studies range from basic to translational research **(Figure 2)**.

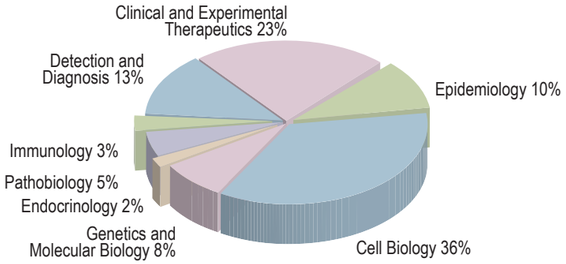
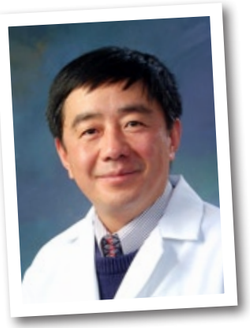


Figure 2. BCRS Award Portfolio Composition

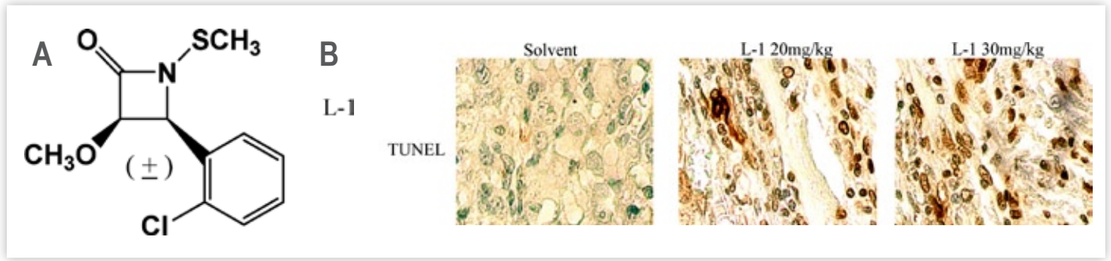
Research Highlights



Synthetic Beta-Lactam Antibiotics as Potential Breast Cancer Therapeutics

Q. Ping Dou, Ph.D., Wayne State University, Detroit, Michigan

For decades, beta-lactam antibiotics have been effective treatments for bacterial infections without causing toxic side effects. A subgroup of this family of antibiotics, termed N-thiolated beta-lactams, was found to inhibit proliferation and induce apoptosis of human tumor cells. Dr. Q. Ping Dou received an FY02 Idea Award to investigate his hypothesis that N-thiolated beta-lactams target a tumor-specific protein and that these drugs can selectively induce apoptosis in human breast cancer, but not normal cells. Modified beta-lactams were designed and synthesized and tested for antiproliferative and pro-apoptotic properties, and then microarray assays were performed to identify target genes. The microarray results revealed a number of potential N-thiolated beta-lactam target genes, including the DNA-interacting proteins GADD45 and Hsp70. These targets were subsequently confirmed by using both breast cancer cell culture and animal models. These results support the hypothesis that beta-lactams cause DNA damage in tumor cells and are potential candidate drugs for breast cancer treatment.

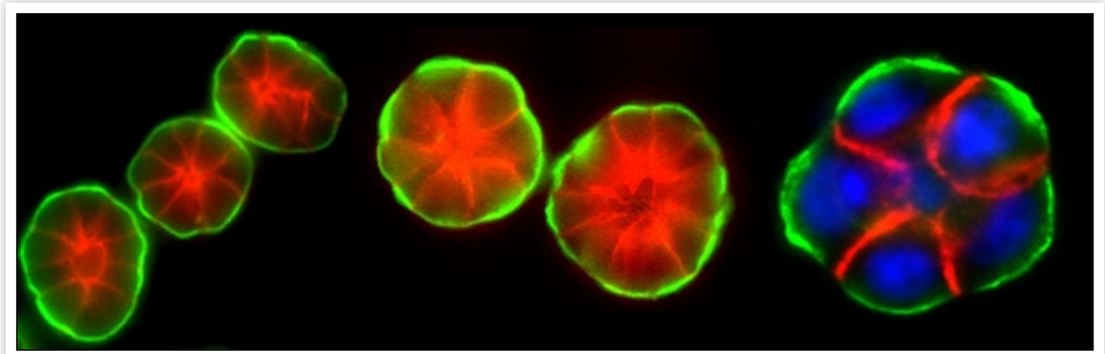


(A) Chemical structure of beta-lactam L-1. (B) Histology of MDA-MB-231 breast tumors from mice after treatment with solvent (control) or two different doses of beta-lactam L-1. Beta-lactam L-1 induces apoptosis in tumors in a dose-dependent manner.

Use of HA-Metal Nanoparticles to Identify and Characterize Tumorigenic Progenitor Cell Subsets in Breast Tumors

Mina J. Bissell, Ph.D., University of California, Berkeley, California, and Dr. Eva Turley, Ph.D., University of Ontario, London, Ontario, Canada

Common breast cancer detection techniques rely primarily on tumor size and cannot be used to identify the cancer subtype or predict drug resistance. Moreover, many current breast cancer treatments are designed to kill rapidly dividing cells and may not effectively kill the slow-growing cancer-initiating (progenitor) cells that give rise to recurrence. Dr. Mina Bissell, recipient of an FY04 Idea Award, and collaborator Dr. Eva Turley have developed hyaluronan (HA) metal (iron, gadolinium, or gold) nanoparticle imaging agents that are selectively and rapidly taken up only by tumor progenitor cells. As different subtypes of breast cancer cells exhibited a different speed of nanoparticle uptake, the investigators assessed the relationship between HA uptake and progenitor cell surface marker profiles. When injected into rat tumor models, the HA-metal nanoparticles were mainly taken up by the liver and the tumor. Additionally, gold-HA nanoparticles were endocytosed by the tumor cells. Furthermore, HA injections were well tolerated in healthy human subjects, which suggests HA's safety as a promising imaging agent for tumorigenic progenitor cell detection.



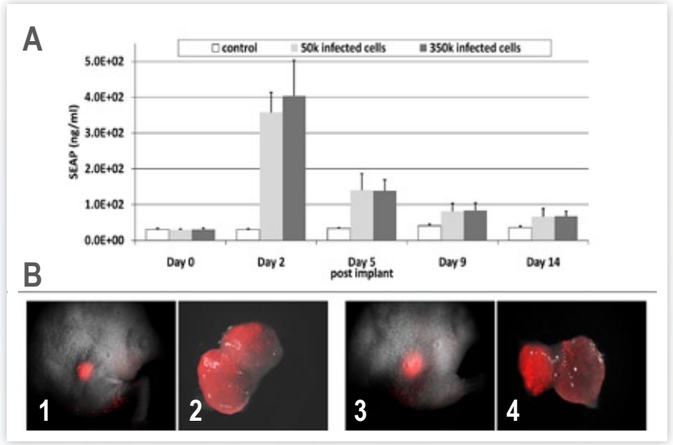
Dr. Bissell's laboratory pioneered the development of in vitro models of breast cancer. Pictured is an acinus, a structural unit of the human breast, which Dr. Bissell's laboratory can reproduce in tissue culture.

Photo credit for picture of Mina Bissell: Roy Kaltschmidt (Lawrence Berkeley National Laboratory)

Novel Screening and Precise Localization of Early Stage Breast Cancer in Animal Models

Kurt R. Zinn, D.V.M., Ph.D., and Jason Warram (Ph.D. student, pictured), University of Alabama at Birmingham, Alabama

Developing more sensitive methods for early detection of breast cancer may improve patient prognosis, as currently available tests do not detect the existence or the location of submillimeter-sized tumors. Serving as Principal Investigator for an FY05 Idea Award, Dr. Kurt Zinn and his student, Jason Warram, have aimed at developing harmless adenovirus vectors that, when injected into breast cancer-carrying mice, infect and induce the production of two proteins in only the cancer cells. One protein, the human placental alkaline phosphatase (SEAP), is secreted into the bloodstream and can be measured through a blood test. The other protein, mCherry, is retained inside the cancer cells while producing red fluorescence, which can be detected from outside of the body via fluorescence imaging, revealing the precise location of the tumor. Animal experiments have revealed that the number and aggressiveness of breast cancer cells correlated with SEAP levels in the blood, and very low numbers of cancerous cells could be detected by their fluorescence noninvasively. Based on the results obtained under this award, Dr. Zinn and Mr. Warram plan on continuing their investigation in a Phase I clinical trial.



(A) Presence of protein SEAP measured in mouse blood plasma; (B) fluorescent images of mCherry in cancer cells: (1) 5.0x10⁴ mCherry-infected tumor cells in mouse hind quarter 2 days post implantation and (2) tumor cells after excision 14 days post implantation. (3) 3.5x10⁵ mCherry-infected tumor cells in mouse hind quarter 2 days post implantation and (4) tumor cells after excision 14 days post implantation.

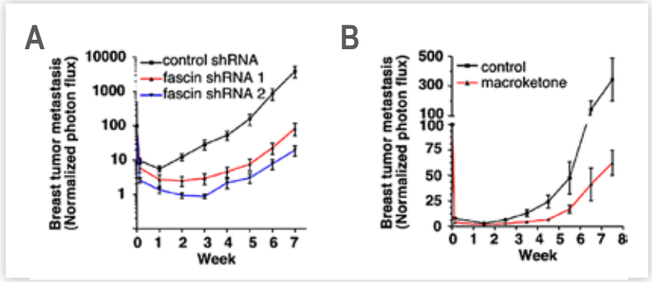
Figure courtesy of Theresa Henson (owner) and permission via University of Alabama at Birmingham.

Migrastatin Analogues as Potent Inhibitors of Breast Cancer Metastasis

Xin-Yun Huang, Ph.D., Cornell University, Weill Medical College, New York, New York

Metastasis is the multistep process wherein a primary tumor spreads from its initial site to secondary tissues/organs. Migrastatin is a macrolide natural product that at high concentrations inhibits the migration of several types of tumor cells. Dr. Xin-Yun Huang, recipient of an FY05 Idea Award, is currently investigating the use of migrastatin analogues as a therapy to prevent breast tumor metastasis.

To develop the potential clinical use of these drugs to inhibit metastasis, Dr. Huang proposed to identify the protein target of migrastatin analogues. He focused on the migrastatin analogue macroketone. His findings revealed that a peptide corresponding to mouse fascin 1 directly interacted with macroketone. Fascin is a critical actin-bundling protein required for cell migration. Given these results, Dr. Huang investigated the ability of macroketone and fascin siRNAs to inhibit metastasis in a mouse model of human breast cancer. In vivo experiments showed both treatments appeared to be effective in blocking human breast tumor metastasis. These results, published recently in *Nature*, highlight the potential for fascin inhibitors to be used as possible therapeutic agents in treating metastatic breast tumors.



Fascin siRNAs and macroketone block human breast tumor metastasis in mouse models. (A) Normalized photon flux of noninvasive bioluminescence images of mice at the indicated dates after injecting human MDA-MB-231 cells expressing control shRNA and two fascin shRNAs. (B) Normalized photon flux of noninvasive bioluminescence images of mice at the indicated dates after injecting human MDA-MB-231 cells in the presence or absence of macroketone (10 mg/kg). Results are mean ± SD.

BCRS Research Funded Awards

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY99	Daly	$283,649	Garvan Institute	Identification of Novel Prognostic Indicators for Breast Cancer Through Analysis of the EMS1/Cortactin Signaling Pathway
	Deuel	$5,000[1]	Scripps Institute	Novel Angiogenic Domains: Use in Identifying Unique Transforming and Tumor-Promoting Pathways in Human Breast Cancer
	Heyer	$111,444	University of California, Davis	In Vitro Recombination Activities of the Breast Cancer Predisposition Protein BRCA2
	Musgrove	$222,652	Garvan Institute	Role of Cyclin D1 and p27 in Steroidal Control of Cell Cycle Progression in the Mammary Gland in Vivo
	Shah	$279,000	University of Arkansas	Role of a Novel Matrix-Degrading Metalloproteinase in Breast Cancer Invasion
	Wang	$317,510	Texas A&M University	Scanning Microwave-Induced Acoustic Tomography
	White	$334,094	University of Texas Southwest Medical Center	Isolation of Factors That Disrupt Critical Protein/Protein Interactions Within the Telomerase Holoenzyme for Use in Breast Cancer Therapeutics
	Wreschner	$225,000	Tel Aviv University	Analysis of the Secreted Novel Breast Cancer-Associated MUC1/Zs Cytokine
FY00	Adamson	$578,183	Burnham Institute	Cripto: A Target for Breast Cancer Treatment
	Akporiaye	$454,500	University of Arizona	Tumor-Mediated Suppression of Dendritic Cell Vaccines
	Penn	$296,142	University of Toronto	Exploiting the Novel Repressed Transactivator Assay to Identify Protein Interactors and Peptide Inhibitors of the Myc Oncoprotein
FY01	Cai	$560,144	Vanderbilt University	Genetic Polymorphisms, Mitochondrial DNA Damage, and Breast Cancer Risk
	Carraway	$427,225	University of California, Davis	Identification of a Functional Human Homolog of Drosophila Kek1, an Inhibitor of Breast Tumor Cell Growth
	Chaudhary	$312,434	University of Texas Southwest Medical Center	The Role of Ectodysplasin A (EDA) and Its Receptors in the Pathogenesis of Breast Cancer
	Geahlen	$425,425	Purdue University	Characterization of Syk in Breast Carcinoma Cells
	Rosner	$454,181	St. Luke's-Roosevelt Hospital Center	Autocrine and Paracrine Control of Breast Cancer Growth by Sex Hormone-Binding Globulin
FY02	Dou	$491,999	University of South Florida	Synthetic Beta-Lactam Antibiotics as a Selective Breast Cancer Cell Apoptosis Inducer: Significance in Breast Cancer Prevention and Treatment
	Godwin	$504,000	Fox Chase Cancer Center	The Nuclear Death Domain Protein p84N5, a Candidate Breast Cancer Susceptibility Gene
	Perkins	$490,500	Yale University	Rapid Genomic Approach to Cancer Gene Discovery in Breast Cancer
FY03	Chung	$490,447	Yale University	Quantitative in Situ Assessment of the Somatostatin Receptor in Breast Cancer to Assess Response to Targeted Therapy with 111-in-Pentetreotide
	Kaaks	$367,639	International Agency for Cancer Research	Fatty Acid Synthesis Gene Variants and Breast Cancer Risk: A Study Within the European Prospective Investigation into Cancer and Nutrition (EPIC)
	Yaswen	$508,790	Lawrence Berkeley National Laboratory	Functional Analysis of BORIS, a Novel DNA-Binding Protein
	Ziv	$767,171	University of California, San Francisco	Admixture and Breast Cancer Risk Among Latinas
FY04	Bissell	$386,569	Lawrence Berkeley National Laboratory	Use of HA-Metal Nanoparticles to Identify and Characterize Tumorigenic Progenitor Cell Subsets in Breast Tumors
	Clarke	$588,738	Northern California Cancer Center	The Hygiene Hypothesis and Breast Cancer: A Novel Application of an Etiologic Theory for Allergies, Asthma, and Other Immune Disorders
	Giorgio	$453,000	Vanderbilt University	Surface Functionalized Nanoparticles and Nanocrystals for Proximity-Modulated, Early Neoplasia Detection, Imaging, and Treatment of Breast Cancer
	Lemmon	$475,500	University of Pennsylvania	Harnessing Novel Secreted Inhibitors of EGF Receptor Signaling for Breast Cancer Treatment
FY05	Zinn[2]	$436,500	University of Alabama at Birmingham	Novel Screening and Precise Localization of Early Stage Breast Cancer in Animal Model
	Huang	$483,600	Cornell University, Weill Medical College	Migrastatin Analogues as Potent Inhibitors of Breast Cancer Metastasis
	Liu	$448,500	Ohio State University	Hunting for Novel X-Linked Breast Cancer Suppressor Genes in Mouse and Human
	Rao	$468,000	Stanford University	Ribozyme-Mediated Imaging of Oncogene Expression in Breast Tumor Cells

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY06	Devi	$155,085[3]	Duke University Medical Center	Modulation of Regulatory T Cells as a Novel Adjuvant for Breast Cancer Immunotherapy
	Lee	$489,000	University of Southern California	A New Mechanism for Estrogen-Starvation Resistance in Breast Cancer
	Li	$438,455	Baylor College of Medicine	The ER/PR Status of the Originating Cell of ER-Negative Breast Cancer
	Mousa	$377,620	Albany College of Pharmacy	Enhancing the Efficacy of Chemotherapeutic Breast Cancer Treatment with Non-Anticoagulant Heparins
	Rastinejad	$454,500	University of Virginia	Structural Characterization of the Interdomain Features of the Estrogen Receptor
FY07	Kuperwasser	$817,500	Tufts University	Mechanisms of Breast Cancer Associated with Obesity
	Kelly	$244,450[4]	Massachusetts General Hospital	Genetically Encoded Targeted, Amplifiable, Imaging Agents for Early Detection of Breast Cancer
	Gerbi	$155,550[5]	Brown University	Hormonal Involvement in Breast Cancer Gene Amplification
FY08	Park	$111,663	North Dakota State University	In Utero Exposure to Dietary Methyl Nutrients and Breast Cancer Risk in Offspring
	Radosz	$528,939	University of Wyoming	Breast Cancer-Targeted Nuclear Drug Delivery Overcoming Drug Resistance for Breast Cancer Therapy
	Hill	$577,500	Oregon Health and Science University	Vaccine Vector for Sustained High-Level Antitumor CTL Response
	You	$503,666	South Dakota State University	Targeted Delivery and Remote-Controlled Release of Chemotherapeutic Agents
	Seagroves	$166,667[6]	University of Tennessee Health Science Center	The Role of HIF-1 Alpha in Breast Cancer: A Positive Factor in Cancer Stem Cell Expansion via Notch?
FY09	Reynolds	$730,000[7]	Cancer Prevention Institute of California	Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk
	Wysolmerski	$620,626	Yale University	Effects of Nuclear Parathyroid Hormone-Related Protein Signaling in Breast Cancer

[1]Award was only partially funded by breast cancer stamp funds; total funding amount for award was $404,176. The DOD BCRP supplied the majority of the funds for the award.

[2]The original Principal Investigator, Dr. Tandra Chaudhuri, is deceased.

[3]Remaining monies for Devi were from the BCRP FY06 funds for a total amount awarded of $461,933.

[4]Award was partially funded with $244,450 of the BCRS funds; the remaining monies are from the FY06 BCRP funds. Total award amount is $687,397.

[5]Award was partially funded with $155,550 of the BCRS funds; the remaining monies are from FY06 and FY07 BCRP funds. Total award amount is $787,325.

[6]Award was partially funded with $166,667 of the BCRS funds; the remaining monies are from FY08 BCRP funds. Total award amount is $554,987.

[7]Award was partially funded with $730,000 of the BCRS funds; the remaining monies are from FY09 BCRP funds. Total award amount is $860,883.

For more information, visit:
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